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Appln. No. 10/049,957

Amd. dated March 30, 2005

Reply to Office Action of June 30, 2004 and March 2, 2005

REMARKS

Claims 1-9 and 11-27 currently appear in this application. The Office Action of June 30, 2004, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicants respectfully request favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

Election/Restrictions

It is noted that claims 7 and 11-15 are withdrawn from further consideration as being drawn to a nonelected group. Accordingly, the claims have been amended to read upon the elected group of the polypeptide SEQ ID NO:4, a polypeptide with MTf activity encoded by a nucleic acid that hybridizes under stringent conditions to nucleic acid encoding SEQ ID NO:4, and to a fragment of SEQ ID NO:4 lacking the GPI anchor region.

Drawings

The drawings are objected to because Figures 2-7 are said to be too dark for the Examiner to reasonably interpret.

Accordingly, submitted herewith are new copies of Figures 2-7.

Claim Objections

Claim 1 is objected to because of the spelling mistake "cartridge." The present amendment corrects this error, and recites a composition containing a chondrogenesis stimulator.

Claims 2 and 3 are said to encompass nonelected inventions. The present amendment corrects this error.

Claims 8-10 are objected to as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claims 8 and 9 have been amended so that they are dependent from claim 1, and claim 10 has been cancelled and replaced by new claim 19.

Rejections under 35 U.S.C. 101

Claims 1-6 and 16 are rejected under 35 U.S.C. 101 because the claimed invention is said to be directed to non-statutory subject matter.

This rejection is respectfully traversed. The claims have now been amended to recite that the protein is an isolated protein.

Rejections under 35 U.S.C. 112

Claims 1-6 and 8-10 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing

to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is respectfully traversed. The claims have now been amended to correct self-evident spelling errors and to include proper dependency. Additionally, claims 2 and 3 have been amended to recite the stringent hybridization defined in the specification at page 9, lines 2-8.

Claim 1 has been amended to recite that the composition comprises a chondrogenesis stimulator.

In claim 2, the DNA hybridizes to a DNA encoding a membrane-bound transferring protein, which can be rabbit p76 protein, human p97 protein; mouse MTF protein, as well as proteins having MTF activity that contain alterations. Support for this can be found in the specification as filed at page 8, line 22-page 9, line 8.

With respect to the MTF activating agent, the specification as filed provides clear instructions as to how to obtain an MTF activating agent. Page 15, beginning at line 14, through page 16, line 8, describes a method for obtaining an activating agent as well as a method to screen compounds for activating activity. One skilled in the art, without undue experimentation, can readily obtain or determine if a compound is an activating agent.

Claim 9 recites" an insulin-like growth factor", which the Examiner alleges is indefinite. It is respectfully submitted that one skilled in the art can readily ascertain what is an insulin-like growth factor.

Submitted herewith are two of many papers found in a GOOGLE search that refer to insulin-like growth factors:

1. Insulin-like Growth Factors in Physiology & Disease, conference February 27-March 4, 2005;
2. PDR Health discussing insulin-like growth factor 1.

Claims 1, 5, 6, 8 and 16 are said to be indefinite because there is said to be no limiting definition of MTf in the specification.

This rejection is respectfully traversed. The specification as filed, beginning at page 4, line 12, discusses MTf protein extensively, and notes that it is preferably a protein having amino acid sequences as defined in the specification, as well as rabbit p76 protein, human p97 protein, mouse MTf protein, as well as a protein demonstrating the MTf activity that has an amino acid sequence encoded by DNA which hybridizes under stringent condition with a DNA that encodes rabbit p76 protein, human p97 protein, or mouse MTf protein. One can readily determine, without undue

experimentation, if a compound is an MTf activating agent following the procedure outlined oat page 6, lines 10-22.

Art Rejections

Claims 1-6, 8-10 and 16 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Jeffries et al.

This rejection is respectfully traversed. Jeffries et al. disclose a protein which is used for modulating iron transport, delivery of therapeutic agents, and in the treatment of conditions involving disturbances of iron metabolism. This protein is also said to be a marker for microglial cells associated with senile plaques. However, there is nothing in Jeffries et al. that discloses or suggests that the protein can be used for stimulating chondrogenesis.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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Insulin-Like Growth Factors In Physiology & Disease

February 27 - March 4, 2005

Holiday Inn

Ventura, CA

Chair: Jeff Holly (University of Bristol, UK)

Vice Chair: Cheryl Conover (Mayo Clinic)

The insulin-like growth factors were originally described as mediators of the effects of growth hormone on the somatic growth of mammals. It has subsequently become clear that they play a more general critical role in integrating growth, development and lifespan according to metabolic conditions. With such a pivotal role, research into IGFs has become of increasing relevance to many of the major health issues currently being addressed including cancer, diabetes, cardiovascular disease, aging and neurodegeneration. This conference will focus on recent developments in IGF-research across a broad range of physiology and pathology, covering aspects from basic biology through to clinical interventions.

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SUNDAY

4:00 pm - 9:00 pm Arrival and Check-in

6:00 pm Dinner

7:30 pm - 9:30 pm **IGFs: History and Future**

Discussion Leader: **Jeff Holly** - University of Bristol, UK

7:30 pm - 8:10 pm **Joe D'Ercole** - UNC, Chapel Hill

Judson Van Wyk Memorial Lecture: "Role of IGF-I in the CNS"

8:10 pm - 8:30 pm Discussion

8:30 pm - 9:10 pm **J. Carl Barrett** - Director of Center for Cancer Research, NCI
"IGF-I and the Biosystem"

9:10 pm - 9:30 pm Discussion

MONDAY

7:30 am - 8:30 am Breakfast

9:00 am - 12:30 pm **Cancer**

Discussion Leader: **Michael Pollak** - McGill University, Canada

9:00 am - 9:30 am **Andrew Hoffman** - Stanford University
"IGF-II, imprinting and Cancer"

9:30 am - 9:40 am Discussion

- 9:40 am - 9:55 am **Brent Sutherland** - Fred Hutchinson Cancer Res Center.
"Defining a critical role for the Insulin-like Growth Factor-1 (IGF-1) axis in prostate homeostasis and cancer in autochthonous genetically engineered mouse systems"
- 9:55 am - 10:00 am Discussion
- 10:00 am - 10:30 am Group Photo / Coffee Break
- 10:30 am - 11:00 am **Shosh Yakar** - NIH, Bethesda
"The role of IGF-I in cancer: evidence from transgenic models"
- 11:00 am - 11:15 am Discussion
- 11:15 am - 11:45 am **Constantine Mitsiades** - Harvard University
"IGF-signalling in multiple myeloma"
- 11:45 am - 12:00 pm Discussion
- 12:00 pm - 12:15 pm **Cynthia Van Golen** - University of Michigan
"The IGF-IR Regulates Bone Metastasis In Human Neuroblastoma"
- 12:15 pm - 12:25 pm Discussion
- 12:30 pm Lunch
- 1:30 pm - 4:00 pm Free Time
- 4:00 pm - 6:00 pm Poster Session
- 6:00 pm Dinner
- 7:30 pm - 9:30 pm **IGF & Bone**
Discussion Leader: **Cliff Rosen** - St. Joseph Hospital, Maine
- 7:30 pm - 8:00 pm **Subburaman Mohan** - Loma Linda, CA
"IGF-system in bone"
- 8:00 pm - 8:15 pm Discussion
- 8:15 pm - 8:45 pm **Tom Clemens** - University Cincinnati
"IGF-system in bone"
- 8:45 pm - 9:00 pm Discussion
- 9:00 pm - 9:15 pm **Cheryl Ackert-Bicknell** - Jackson Laboratory
"A polymorphism in the P1 promoter of IGF-1 may be responsible for IgfsI2: a gender specific quantitative trait locus for serum IGF-1 associated with multiple and complex bone phenotypes"
- 9:15 pm - 9:25 pm Discussion

TUESDAY

- 7:30 am - 8:30 am Breakfast
- 9:00 am - 12:30 pm **Diabetes & Cardiovascular Disease**
Discussion Leader: **David Clemmons** - UNC, Chapel Hill
- 9:00 am - 9:30 am **Alan Moses** - Princetown, New Jersey
"Using IGF-I to normalise the GH/IGF-system"
- 9:30 am - 9:45 am Discussion
- 9:45 am - 10:15 am **Peter Bang** - Karolinska Hospital, Stockholm, Sweden
"Using Insulin glargine to normalise the GH/IGF-system"
- 10:15 am - 10:30 am Discussion
- 10:30 am - 11:00 am Coffee Break
- 11:00 am - 11:30 am **Patrice Delafontaine** - Tulane University
"IGFs and Cardiovascular Disease"
- 11:30 am - 11:45 am Discussion
- 11:45 am - 12:00 pm **Laura Maile** - Chapel Hill
"Calpain dependent clustering of the V β 3 integrin with the transmembrane proteins IAP and SHPS-1 is necessary for Shc phosphorylation and MAP kinase activation in response to IGF-I"
- 12:00 pm - 12:05 pm Discussion

- 12:05 pm - 12:20 pm **Adam Denley** - Adelaide
 "Differential activation of insulin receptor isoforms by insulin-like growth factors is determined by the IGF C domain"
- 12:20 pm - 12:30 pm Discussion
- 12:30 pm Lunch
- 1:30 pm - 4:00 pm Free Time
- 4:00 pm - 6:00 pm Poster Session
- 6:00 pm Dinner
- 7:30 pm - 9:30 pm **IGF-I & Growth**
 Discussion Leader: **Peter Rotwein** - Oregon Health Sci University
- 7:30 pm - 8:00 pm **Bob Smith** - Brown Medical School, Rhode Island
 "Heterozygous IGF-I receptor mutations in humans"
- 8:00 pm - 8:15 pm Discussion
- 8:15 pm - 8:45 pm **Ron Rosenfeld** - San Francisco
 "IGF-I deficiency: new paradigms"
- 8:45 pm - 9:00 pm Discussion
- 9:00 pm - 9:15 pm **Laurie Bale** - Mayo Clinic
 "Disruption of Insulin-Like Growth Factor-II Imprinting During Embryonic Development Rescues The Dwarf Phenotype of Mice Null for Pregnancy-Associated Plasma Protein-A"
- 9:15 pm - 9:25 pm Discussion
- WEDNESDAY**
- 7:30 am - 8:30 am Breakfast
- 9:00 am - 12:30 pm **IGFBPs**
 Discussion Leader: **Rob Baxter** - Kolling Inst Med Res, Australia
- 9:00 am - 9:30 am **Leon Bach** - University of Melbourne, Australia
 "Structure function of IGF/IGFBP interactions"
- 9:30 am - 9:45 am Discussion
- 9:45 am - 10:15 am **Cunming Duan** - University of Michigan
 "IGFBP-5 actions"
- 10:15 am - 10:30 am Discussion
- 10:30 am - 11:00 am Coffee Break
- 11:00 am - 11:30 am **Liam Murphy** - University of Manitoba, Winnipeg
 "Use of transgenic models for elucidating IGFBP-function"
- 11:30 am - 11:45 am Discussion
- 11:45 am - 12:00 pm **Klaus Frommer** - Tuebingen
 "IGFBP-2 Mediated Cellular Gene Expressions and Effects of IGFBP-2 on Apoptosis"
- 12:00 pm - 12:05 pm Discussion
- 12:05 pm - 12:20 pm **Jennifer Kricker** - Queensland Univ.
 "Functional analysis of the impact of glycosylation and heparin-binding regions of IGFBPs on the interaction of IGF-I with vitronectin"
- 12:20 pm - 12:30 pm Discussion
- 12:30 pm Lunch
- 1:30 pm - 4:00 pm Free Time
- 4:00 pm - 6:00 pm Poster Session
- 6:00 pm Dinner
- 7:30 pm - 9:30 pm **Nervous System**
 Discussion Leader: **Terri Wood** - Penn State College of Medicine
- 7:30 pm - 8:00 pm **Eva Feldman** - University of Michigan
 "IGFs and neuroblastoma"

- 8:00 pm - 8:15 pm Discussion
- 8:15 pm - 8:45 pm **Kim Heidenreich** - University of Colorado
"IGFs and neurons"
- 8:45 pm - 9:00 pm Discussion
- 9:00 pm - 9:15 pm **Friedrich Metzger** - Hoffman-La Roche, Switzerland
"Therapeutic Actions of IGF-I in an Alzheimer Mouse Model with Severe Brain Amyloidosis"
- 9:15 pm - 9:25 pm Discussion

THURSDAY

- 7:30 am - 8:30 am Breakfast
- 9:00 am - 12:30 pm **Cancer Signalling and Targeting**
Discussion Leader: **Derek LeRoith** - NIH, Bethesda
- 9:00 am - 9:30 am **Pinchas Cohen** - UCLA
"IGFs and Prostate Cancer"
- 9:30 am - 9:45 am Discussion
- 9:45 am - 10:15 am **Doug Yee** - University of Minnesota
"Targeting the IGF-system in breast cancer"
- 10:15 am - 10:30 am Discussion
- 10:30 am - 11:00 am Coffee Break
- 11:00 am - 11:15 am **Mark Pearson** - Novartis Institute for Biomed. Res. Basel, Switzerland
"Identification and characterisation of a specific small molecular weight IGFIR tyrosine kinase inhibitor"
- 11:15 am - 11:20 am Discussion
- 11:20 am - 11:35 am **Jack Youngren** - UCSF/MT. Zion Med. Cent.
"Insm-18 inhibits the IGF-I receptor in breast cancer cells"
- 11:35 am - 11:40 am Discussion
- 11:40 am - 11:55 am **Antonio Gualberto** - Pfizer, New London, CT
"Inhibition of IGF-IR by a specific monoclonal antibody"
- 11:55 am - 12:00 pm Discussion
- 12:00 pm - 12:15 pm **Jonathan Pachter** - Schering-Plough Res. Inst. Kenilworth, NJ
"Antitumor efficacy of a fully human anti-IGF-IR neutralising antibody and preclinical validation of markers"
- 12:15 pm - 12:20 pm Discussion
- 12:20 pm - 12:30 pm General Discussion
- 12:30 pm Lunch
- 1:30 pm - 4:00 pm Free Time
- 4:00 pm - 6:00 pm Poster Session
- 6:00 pm Dinner
- 7:30 pm - 9:30 pm **Aging & Lifespan**
Discussion Leader: **Cheryl Conover** - Mayo Clinic
- 7:30 pm - 8:10 pm **Christian Sell** - Lankenau Institute, PA
"IGF and Aging; does more mean less, or less mean more?"
- 8:10 pm - 8:30 pm Discussion
- 8:30 pm - 9:10 pm **Heidi Scoble** - University of Virginia School of Medicine
"p53, tumour suppression and aging"
- 9:10 pm - 9:30 pm Discussion
- FRIDAY**
- 7:30 am - 8:30 am Breakfast
- 9:00 am Depart

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Insulin-Like Growth Factor 1 (IGF-1)

DESCRIPTION

Insulin-like growth factor-1 (IGF-1) is a single-chain polypeptide of 70 amino acids. It is a trophic factor that circulates at high levels in the blood-stream and mediates many, if not most, of the effects of growth hormone. Although the main source of IGF-1 in the serum is the liver, many other tissues synthesize it and are sensitive to its trophic action. IGF-1 was called somatomedin in the older literature. IGF-1 and insulin have similar three-dimensional structures.

IGF-1 appears to influence neuronal structure and functions throughout the life span. It has been shown to have the ability to preserve nerve cell function and promote nerve growth in experimental studies. Because of these properties, recombinant human IGF-1 is in clinical trials for the treatment of amyotrophic lateral sclerosis (ALS).

Recently, recombinant human IGF-1 has entered the dietary supplement marketplace, as have recombinant human growth hormone and several so-called growth hormone secretagogues or releasers.

ACTIONS AND PHARMACOLOGY

ACTIONS

Supplemental IGF-1 has putative anabolic and lipolytic activities.

MECHANISM OF ACTION

The mechanism of the putative actions of supplemental IGF-1 is unknown.

PHARMACOKINETICS

Orally administered IGF-1 has very poor bioavailability. There is no credible evidence that IGF-1 is absorbed from the oral mucosa if administered as a spray. It is likely that orally administered IGF-1 is digested in the small intestine to the amino acids that comprise the molecule.

INDICATIONS AND USAGE

Claims for supplemental IGF-1 are sweeping and include antiaging, promotion of lean muscle mass, enhanced athletic and sexual performance, joint protection, antidiabetic and antiatherosclerotic effects, sleep aid, immune enhancer, neuroprotector and much more. There is no credible evidence to support these claims for oral IGF-1. High levels of IGF-1 have been associated with elevated risk of several cancers, especially prostate cancer.

RESEARCH SUMMARY

There is no research to support the use of IGF-1 as a nutritional supplement, whether in oral or injected form. There is research showing associations between high levels of circulating IGF-1 and several cancers.

Claims that IGF-1 supplements significantly increase lean muscle mass are unsubstantiated. Use of IGF-1 in doses far higher than those used by most bodybuilders failed to produce more than very modest anabolic effects in AIDS patients. It is possible that some clinical indications, but not supplemental indications, will emerge from experimental work currently underway with IGF-1. There is a hint in some of this work that IGF-1 might, for

example, have some neuroprotective and neurorestorative effects in some conditions.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Supplemental IGF-1 is contraindicated in those with any evidence of active malignancy. It is also contraindicated in those who are hypersensitive to any component of an IGF-1-containing product.

PRECAUTIONS

Pregnant women and nursing mothers should avoid the use of supplemental IGF-1-containing products.

Adolescents should avoid the use of supplemental IGF-1-containing products.

Supplemental IGF-1 is not meant to be used parenterally and should never be used in such a manner.

ADVERSE REACTIONS

None known for supplemental IGF-1-containing supplements.

INTERACTIONS

There are no known interactions for supplemental IGF-1-containing supplements.

OVERDOSAGE

No reports for supplemental IGF-1-containing supplements.

DOSAGE AND ADMINISTRATION

Supplemental IGF-1 is available and marketed as a dietary supplement, typically in the form of an oral spray. There are no recommended doses.

LITERATURE

Carro E, Nuñez A, Busiguina S, Torres-Aleman I. Circulating insulin-like growth factor 1 mediates effects of exercise on the brain. *J Neurosci*. 2000; 20:2926-2933.

Chan JM, Stampfer MJ, Giovannucci E, et al. Plasma insulin-like growth factor 1 and prostate cancer risk: a prospective study. *Science*. 1998; 279:563-566.

Giovannucci E, Pollak MN, Platz EA, et al. A prospective study of plasma insulin-like growth factor-1 and binding protein-3 and risk of colorectal neoplasia in women. *Cancer Epidemiol Biomarkers Prev*. 2000; 9:345-349.

Hankinson SE, Willett WC, Colditz GA, et al. Circulating concentrations of insulin-like growth factor-1 and risk of breast cancer. *Lancet*. 1998; 351:1393-1396.

Le Roith D. Insulin-like growth factors. *N Engl J Med*. 1997; 336:633-640.

Lewis ME, Neff NT, Contreras PC, et al. Insulin-like growth factor-1: potential for treatment of motor neuronal disorders. *Exp Neurol*. 1993; 124:73-88.

Magee BA, Shooter GK, Wallace JC, Francis GL. Insulin-like growth factor 1 and its binding proteins: a study of the binding interface using B-domain analogues. *Biochem*. 1999; 38:15863-15870.

Mantzoros CS, Tzonou A, Signorello LB, et al. Insulin-like growth factor 1 in relation to prostate cancer and benign prostate hyperplasia. *Brit J Cancer*. 1997; 76:1115-1118.

Niblock MM, Brunso-Bechtold J, Riddle DR. Insulin-like growth factor 1 stimulates dendritic growth in primary somatosensory cortex. *J Neurosci.* 2000; 20:4165-4176.

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